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EXAMINER
CAPUTA, A

18N1/1019

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ART UNIT	PAPER NUMBER
1813	14

DATE MAILED: 10/19/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 2pgs
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-20 are pending in the application.
   Of the above, claims 4-6 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 7-20 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
    ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Part III DETAILED ACTION

1. Preliminary Amendment (Paper No. 12) was entered.

Objections

2. The use of trademarks such as RPMI 1640 (see page 27, last paragraph), Dynatech MR5000 ELISA plate reader (see page 11, first paragraph), etc. have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Election/Restriction

4. Applicant's election of peptides 482(481) and 484; Seq I.D. no. 70 in Paper No. 11 of claims 1-11 and 17-20 is acknowledged. Upon further consideration Groups I-III (claims 1-20) are considered a single invention. Because applicant did not distinctly and specifically point out the supposed errors in the

restriction requirement (See Paper No. 11), the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

5. In view of the applicant election of peptides 482(481) and 484, claims 4, 5, and 6 are withdrawn from consideration in view that the epitopes as claimed encompass peptides of different proteins (e.g. LA/SSB and Sm B/B') and/or different amino acid composition.

Double Patenting

6. Claims 1-3 and 7-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-17, 26, 29, 31, 56, and 64 of copending application Serial No. 07/648,205. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass equivalent peptides with the method of use for treatment and diagnosis.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37

C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Claim Rejections - 35 USC § 112/2nd paragraph

8. Claims 1-3, and 7-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-3, and 7-20 are vague and indefinite in view that it is unclear if the applicant is claiming peptides or the epitope. For instance it is unclear if the peptide or epitope is administered to a host, immobilized onto the substrate, etc. It is suggested that peptide be claimed and not the epitope.

b. Claims 7-11 are rejected for lack of antecedent basis for claiming epitopes in view that the independent claim, claim 1 is claiming a singular epitope.

c. Claim 2 is rejected in view that the elected species consists of fixed number of amino acids and not between 4 and 25 amino acids as claimed.

d. Claim 16 is unclear for the use of the term prognosis in view that it can be defined serologically and/or clinically (i.e. clinical signs).

Claim Rejections - 35 USC § 101

9. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

10. Claims 1-3, 7-20 are rejected under 35 U.S.C. § 101 because the claimed invention as disclosed lacks patentable utility.

The specification provides insufficient evidence that the peptide can be used as a vaccine, treatment and diagnosis. The specification provides evidence of the reaction of the elected peptide of normal sera and sera from patients which react with the Ro/SSA protein, however the specification provides insufficient guidance if the reactivity of the peptide with the sera from patients with Ro/SSA is significantly different from normal sera (see Example 2 and Table 2). Further the specification provides no evidence that the epitope is protective in vivo or in vitro. The specification provides no evidence to what extent the peptide (or epitope) is recognized with patients that react with the Ro/SSA protein (1, 2, 10, 50, 95%) and if this epitope is involved in the pathogenesis or protection. The disclosure provides insufficient evidence to the extent the peptide is recognized by sera with patients that have SLE or other diseases and further if the epitope is found in other proteins of other origin which may not be associated with said

diseases (i.e., N protein of VSV; see Scofield and Harley, PNAS, 1991). Without evidence that the peptide is protective in vivo or useful for treatment one of ordinary skill in the art would not use the peptide in the administration of patients as claimed (see claims 7, 8, 9 and 17-20), especially in view that the autoantibodies are implicated in autoimmune disease (see Dryberg et al.) and there is insufficient guidance as to whether the epitope is protective or directly responsible for pathogenesis.

The difficulty in predicting whether a particular in vitro test will be predictive of an asserted in vivo activity has long been recognized. Pharmaceutical therapy is unpredictable in the absence of in vivo clinical data for the reasons described above and for the following reasons:

(1) The protein (peptide) may be inactivated before producing an effect, e.g. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) The protein may otherwise not reach the target area because for example, (a) the protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect, and (c) circulation to or in the target area may be insufficient to carry the peptide; (3) A large enough effective local concentration may not be capable of being established; and (4) Other functional properties, known and unknown, may make the protein unsuitable for in vivo use, i.e. may produce adverse side effects prohibitive to the use of such treatment. See M.P.E.P. 608.01(P). See In re Carroll, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979). When the utility of a product is directed to humans, the data must generally be clinical. In order to accept animal data, there must exist an art recognized model for testing purposes. See In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962). It is well established that a patent may not be granted on a composition unless a utility is shown other than for experimental purposes only. The burden is on the applicant to demonstrate that the claimed products posses the claimed biological activity. See Brenner v Manson 383 U.S. 519, 148 USPQ 689 (1966).

Claim Rejections - 35 USC § 112/1st paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

a. The specification is not enabled for the use of the claimed invention because the utility of the invention has not been proven for the same reasons outlined in the rejection under 35 U.S.C. § 101.

The specification further fails to teach how to use the claimed peptide for treatment or diagnosis, how to formulate the pharmaceutical composition and guidance to the method of treatment or diagnosis. The specification fails to provide substantive <u>in vivo</u> evidence or a working example that the administration of peptides results in the desired immune response. The specification fails to provide evidence that the peptide is specific for diagnosis and the extent that the peptide is recognized from the sera of patient with autoimmune

disease(s). The specification further fails to provide the information required to use the protein such as the amount of protein to administer, the method of administration, the frequency of administration, etc. as a vaccine or for binding and neutralization of autoantibodies. Accordingly it would require undue experimentation for one of ordinary skill in the art to use the protein, and methods to achieve the desired response for treatment or use for diagnosis.

b. The specification provides evidence of two octapeptides beginning with the amino acid numbered 481-484-489 that are recognized by anti-Ro/SSA (see Table 2). The specification however provides insufficient evidence to which region of the octapeptide recognizes the antibody and peptides of up to 40 amino acids in length as claimed. It would not have been expected that all the peptides (i.e. 4-7 amino acids in length) would have been useful as claimed in view that the peptides would not share the same amino acid composition and therefore the epitope which recognizes the antibody as claimed. In view that the applicant's have provided no guidance beyond octapeptides it would have been undue experimentation to determine which portions of the peptides recognize the epitope as claimed.

Further in view that the additions of amino acids to the peptide alter tertiary structure and the recognition of antibody to the antigen it would have been undue experimentation to determine which additions to the octapeptides would not affect

the structure and binding of the peptide to the antibody (i.e. epitope) that encompass the peptides as broadly claimed.

c. With regards to claim 16 the specification provides evidence that sera of patients with a reaction to the 60 kDa protein react with the elected species at greater than a fixed value and less than this value with normal sera. The specification however provides no guidance of the reaction of the elected peptides to autoantibodies and the prognosis of the patient. In view that the specification provides no guidance to the specificity, variability, and how reactivity of the elected peptides and antibody is related the severity of the disease(s) it would be an undue burden to ascertain the use of the method to predict the prognosis of the patient as claimed.

12. Claims 1-3, and 7-20 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

> Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

14. Claims 1-3, 8, 10-17, 19, and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Deutscher et al., in view of Harley (U.S. Patent No. 4,784,942), Dryberg et al., Geysen et al. and Voller et al.

Deutscher et al. teaches of the amino acid sequence of the 60 kDa human ribonucleoprotein that the recombinant protein is useful for the detection of autoantibodies in the sera of patients with autoimmune disorders (see Abstract and Figure 5). Deutscher et al. does not disclose of the composition of the peptides 482 and peptides 484.

Harley teaches that the use of immunogenic fragments against proteins such as Ro/SSA reduce unwanted sample interactions and minimize unwanted background (see Column 5, lines 30-35).

Dryberg et al. teaches that antigenic determinants shared by infectious agents and host proteins could be responsible for the autoimmune response (see Introduction). Dryberg et al. teaches that the shared antigenic determinants can be determined by the homology between the sequences.

Geysen et al. teaches of a method to identify antigenic determinants by testing antibody reactivity against a set of overlapping peptides representing the sequence of the protein.

Voller et al. teaches of an indirect method using the ELISA assay to determine the antibody that is found in the sera by immobilizing the antigen on a substrate such as a plate and a sandwich method to determine the antibody by immobilizing the antigen on the plate and an antigen which is enzyme labeled (see pages 99-101).

It would have been obvious to use the method of Geysen et al. to identify those peptides of the human Ro protein as described by Deutscher et al. that share homology with infectious agents and are specifically responsible for the autoimmune response as suggested by Dryberg et al. and use the fragments of Ro/SSA as disclosed by Deutscher et al. in the assay for the detection of antibody as disclosed by Voller et al. in view that as disclosed by Harley et al. the use of fragments reduce unwanted background for diagnosis. In view that the synthetic peptides can be made readily chemically it would have been obvious to one of ordinary skill in the art to use the method of Geysen et al. to determine the epitope of the protein as disclosed by Deutscher et al. and use the synthetic peptides for treatment as claimed, since it would have been expected that the peptide would bind the autoantibody which are associated with the

autoimmune disease as suggested by Deutscher et al. and Dryberg et al.

15. Claims 1-3, and 7-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Deutscher et al., in view of Harley (U.S. Patent No. 4,784,942), Hopp (U.S. Patent No. 4,554,101), and Voller et al.

Deutscher et al. teaches of the amino acid sequence of the 60 kDa human ribonucleoprotein that the recombinant protein is useful for the detection of autoantibodies in the sera of patients with autoimmune disorders (see Abstract and Figure 5). Deutscher et al. suggests that the etiology of the autoimmune disease is infectious agents and that antibodies are correlated with the pathogenesis (see page 9479). It would have been obvious to one of ordinary skill in the art that in view that infectious agents are implicated in the etiology of autoimmune diseases as described by Deutscher et al. that antibodies to the 60 KDa protein would be useful in the prevention of autoimmune disease associated with 60 kDa protein.

Harley teaches that the use of immunogenic fragments against proteins such as Ro/SSA reduce unwanted sample interactions and minimize unwanted background (see Column 5, lines 30-35).

Voller et al. teaches of an indirect method using the ELISA assay to determine the antibody that is found in the sera by immobilizing the antigen on a substrate such as a plate and a

sandwich method to determine the antibody by immobilizing the antigen on the plate and an antigen which is enzyme labeled (see pages 99-101).

Hopp teaches of a method of determining the epitopes of antigen on the basis of hydrophilicity by using the amino acid sequence of antigen (see Column 1 and 2; and claims 1-6). Hopp teaches that antigens encompass autoantigens responsible for autoimmune diseases (see Column 18, lines 25-29), Hopp teaches that the peptides containing the eptiopes can be used as synthetic vaccines with a carrier (see Columns 1, 2, and 14). Hopp teaches that the peptide can have a length of six amino acids with preferably a length not greater than 40 amino acids (see Columns 4 and 5; especially Column 5, line 8). Hopp teaches that the present invention can be used in a RIA or ELISA (see Column 15 and 16). Hopp et al. teaches that the synthetic vaccine can contain a combination of epitopes (see Column 3, lines 35-45). In view that the synthetic peptides can be made readily by Merrifield Chemical synthesis (see Hopp, Column 12 and 13) it would have been obvious to one of ordinary skill in the art to use the method of Hopp to determine the epitope of the protein as disclosed by Deutscher et al. and use the synthetic peptides in a vaccine with a carrier as disclosed by Hopp. In view that the peptides as determined by Deutscher et al. in view of Hopp are likely to reduce unwanted background and enhance sensitivity as disclosed by Harley it would have been obvious to

one of ordinary skill in the art to use the peptides for the detection of autoantibodies in the assay for the detection of antibody as disclosed by Voller et al. Further it would have been expected that the peptide would bind the autoantibody as claimed as suggested by Hopp (see Column 4, lines 53-62) and therefore be useful for treatment of the autoimmune disease by binding the autoantibodies found in the serum which are associated with the autoimmune disease as suggested by Deutscher et al. It would have been expected that the peptides would have been useful as a vaccine and elicit an antibody response which would be effective against the infectious agents that play a role in the autoimmune diseases as suggested by Deutscher et al.

Thus the claimed invention as a whole is clearly prima facie obvious, especially in the absence of evidence to the contrary.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Barakat et al. teaches of two C-terminal fragments (495-518, and 524-538) had no antigenic activity (see Discussion, 1st paragraph).

Ben-Chetrit et al. teaches of the cDNA sequence of the 60 kDA SSA/Ro protein.

Frank et al. (WO 91/17171) teaches that portions of the Ro/SSA antigen are useful for diagnosis and for treatment.

17. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4227.

Anthony C. Caputa, Ph.D.

October 15, 1993

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